A Rare Human Syndrome Provides Genetic Evidence that WNT Signaling Is Required for Reprogramming of Fibroblasts to Induced Pluripotent Stem Cells.

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Public Summary:
This study demonstrates that the process of generating embryonic-like stem cells, also known as induced pluripotent stem (iPS) cells, requires the contribution of a highly conserved signaling pathway, called WNT (pronounced "wint"). Without WNT signaling, iPS cells can not be established from mature cell types, such as skin fibroblasts. The key evidence for this finding came from the use of cell biopsies from patients with an extremely rare genetic disorder, called focal dermal hypoplasia (FDH). FDH patients carry a mutation in a gene, called PORCN, the activity of which is essential for WNT signaling. These findings provide important insights into the mechanism by which iPS cells are generated, and offer novel strategies to improve frequencies for the generation of iPS cells. In addition, these results indicate a critical role for WNT signaling in regenerative processes, such as tissue repair and wound healing.

Scientific Abstract:
WNT signaling promotes the reprogramming of somatic cells to an induced pluripotent state. We provide genetic evidence that WNT signaling is a requisite step during the induction of pluripotency. Fibroblasts from individuals with focal dermal hypoplasia (FDH), a rare genetic syndrome caused by mutations in the essential WNT processing enzyme PORCN, fail to reprogram with standard methods. This blockade in reprogramming is overcome by ectopic WNT signaling and PORCN overexpression, thus demonstrating that WNT signaling is essential for reprogramming. The rescue of reprogramming is critically dependent on the level of WNT signaling: steady baseline activation of the WNT pathway yields karyotypically normal iPSCs, whereas daily stimulation with Wnt3a produces FDH-iPSCs with severely abnormal karyotypes. Therefore, although WNT signaling is required for cellular reprogramming, inappropriate activation of WNT signaling induces chromosomal instability, highlighting the precarious nature of ectopic WNT activation and its tight relationship with oncogenic transformation.